

What is claimed is:

1. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release  
5 Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the  
10 form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem  
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(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:  
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  - (a) between about 1% and about 15% after 2 hours;
  - (b) between about 7% and about 35% after 4 hours;
  - (c) between about 30% and about 58% after 8 hours;
  - (d) between about 55% and about 80% after 14 hours; and
  - (e) and in excess of about 75% after 24 hours.

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and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- 5 (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours.

2. A method of treating or preventing myocardial ischemia and angina in  
10 a patient in need thereof comprising administration of a controlled-release  
Galenical preparation of pharmaceutically acceptable form of Diltiazem  
including the pharmaceutically acceptable salts thereof, for evening dosing  
every 24 hours containing from about 180 mg to about 420 mg of the form of  
Diltiazem with excipients to provide controlled (sustained) release of the  
15 form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in  
the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after  
administration, the preparation being in a sustained-release dosage form in  
which the form of Diltiazem is adapted to be control released after  
administration of the preparation over a period of time and being adapted to  
20 release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the  
method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of  
water:

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- (a) between about 4% and about 8% after 2 hours;

- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

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and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;
- 10 (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours.

3. The method of claim 1 wherein the  $C_{max}$  of Diltiazem in the blood is  
15 obtained between about 11 - about 13 hours after administration of the preparation.

4. The method of claim 2 wherein the  $C_{max}$  of Diltiazem in the blood is  
obtained between about 11 - about 13 hours after administration of the  
20 preparation.

5. The method of claim 1 wherein the preparation is a diffusion  
controlled preparation.

6. The method of claim 1, wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
- 5 7. The method of claim 1, wherein the preparation is in capsule form.
8. The method of claim 1, wherein the preparation is in tablet form.
- 10 9. The method of claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
- 15 10. The method of claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and
- 20 the central core comprises the form of Diltiazem or pharmaceutically

acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

11. The method of claim 1 wherein the preparation comprises a  
5 plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent  
10 assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15 12. The method of claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the  
20 membrane comprises a water-dispersible or water-soluble polymer and a

water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

- 5    13.    The method of claim 1                    wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the  
10    preparation comprises a mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which  
15    hydrates the preparation.

14.    The method of claim 1                    wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and  
20    the central core comprises the form of Diltiazem or pharmaceutically

acceptable salt thereof associated with a wetting agent wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

5 15. The method of claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the  
10 membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

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16. The method of claim 9 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate, an acrylic polymer and  
20 plasticizer combined to form the membrane thereby providing a mechanism

of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

5 17. The method of claim 1 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in  
10 the release of the form of Diltiazem from the preparation.

18. The method of claim 1 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core  
15 comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which  
20 permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.



19. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of said preparation of claim 1 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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20. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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21. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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22. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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23. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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24. A method of treating myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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25. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 7 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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26. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 8 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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27. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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28. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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29. A method of treating or preventing myocardial ischemia in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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30. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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31. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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32. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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33. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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34. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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35. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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36. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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37. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of said preparation of claim 1 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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38. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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39. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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40. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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41. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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42. A method of treating myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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43. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 7 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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44. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 8 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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45. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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46. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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47. A method of treating or preventing myocardial ischemia in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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48. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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49. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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50. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour

10 period.

51. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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52. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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53. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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54. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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55. The method of claim 1 wherein the preparation contains 180 mg of Diltiazem.

56. The method of claim 1 wherein the preparation contains 360 mg of Diltiazem.

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57. The method of claim 1 wherein the preparation contains 420 mg of Diltiazem.

15 58. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of

20 Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control

25 released after administration of the preparation over a period of time and being adapted to release the Diltiazem



(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- 5           (a) between about 1% and about 15% after 2 hours;  
             (b) between about 7% and about 35% after 4 hours;  
             (c) between about 30% and about 58% after 8 hours;  
             (d) between about 55% and about 80% after 14 hours; and  
             (e) and in excess of about 75% after 24 hours.

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and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;  
15           (b) between about 7% and about 45% after about 4 hours;  
             (c) between about 30% and about 68% after about 8 hours;  
             (d) in excess of about 75% after about 24 hours wherein the  
preparation comprises a plurality of microgranules, wherein each  
microgranule comprises a central core of the form of diltiazem or a  
20           pharmaceutically acceptable salt thereof, associated with a wetting agent,  
             wherein the central core is coated with a microporous membrane and  
             wherein the wetting agent is selected from the group consisting of:

sugars;

- 25           saccharose, mannitol, sorbitol;  
             lecithins;

C<sub>12</sub> to C<sub>20</sub> fatty acid esters of saccharose,;  
xylose esters or xylites;  
polyoxyethylenic glycerides;  
esters of fatty acids and polyoxyethylene;  
5 sorbitan fatty acid esters;  
polyglycides-glycerides and polyglycides-alcohols esters and  
Metal salts.

59. The method of claim 9 wherein the wetting agent is in association with  
10 the diltiazem in the microgranule and not mixed therewith, the membrane  
comprises a water-soluble or water dispersible polymer or copolymer and a  
water-, acid- and base-insoluble polymer which is a neutral copolymer of  
acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be  
hydrated by the introduction of intestinal fluids into the core hydrating the  
15 core and therefore mixing the diltiazem and the wetting agent.

60. A method of treating or preventing myocardial ischemia and angina in  
a patient in need thereof comprising the administration of the preparation of  
claim 58 to the patient in the evening for effective treatment or prevention of  
20 the patient's myocardial ischemia and angina the next morning.

61. A method of treating or preventing myocardial ischemia and angina in  
a patient in need thereof comprising the administration of the preparation of  
claim 3 to the patient in the evening for effective treatment or prevention of  
25 the patient's myocardial ischemia and angina the next morning wherein each  
microgranule comprises a central core of the form of diltiazem or a

pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-  
5 soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

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62. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period  
15 wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-  
20 soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

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63. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;

- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

10		% W/W
	(a) Diltiazem hydrochloride	69 - 73
	(b) Microcrystalline cellulose	8 - 9.5
	(c) Povidone K30	1 - 2
	(d) Sucrose stearate	7 - 8
15	(e) Magnesium stearate NF	0.5 - 2.5
	(f) Talc USP	0.5 - 5.0
	(g) Titanium dioxide (USP)	0.15 - 0.3
	(h) Hydroxypropylmethylcellulose 2910	0.3 - 0.6
	(i) Polysorbate 80 (tween)	0.01 - 0.025
20	(j) Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
	(k) a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

- 25 64. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of

claim 63 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

5 65. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 63 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

10 66. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing about 180 mg to about 420 mg of the form of  
15 Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released  
20 after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

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(a) between about 1% and about 15% after 2 hours;

- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

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and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- 10 (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a
- 15 pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

- (i) in the core,

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- (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

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- (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

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(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

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(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

67. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of  
15 claim 65 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

68. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of  
20 claim 65 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

69. A method of treating or preventing myocardial ischemia and angina in  
25 a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem



including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

10 (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- 15 (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

20 and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- 25 (c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent,  
5 wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

10 (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of  
15 the total preparation);

together with adjuvants; and

(ii) in the membrane,

20

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

5 70. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 69 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

10 71. The method of claim 9 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

15

72. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 71 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

20

73. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 71 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour  
25 period.

74. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

5 (c) between about 0.1% and about 2% of the total preparation  
of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the  
preparation) of a neutral copolymer of acrylic acid ethyl ester  
10 and acrylic acid methyl ester, together with adjuvants.

75. The method of claim 74 wherein the microgranules are in capsule form.

76. The method of claim 74 wherein the microgranules are in tablet form.

15

77. The method of claim 74 wherein the core and membrane  
comprise:

(i) in the core,

20

(a) between about 69% and about 73% (% w/w of the total  
preparation) of Diltiazem or pharmaceutically acceptable salt  
thereof; and

25 (b) between about 7% and about 8% wetting agent (% w/w of  
the total preparation);

together with adjuvants; and

(ii) in the membrane,

5

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

10

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

78. A method of treating or preventing myocardial ischemia and angina in  
15 a patient in need thereof comprising administration of a controlled-release  
Galenical preparation of pharmaceutically acceptable form of Diltiazem  
including the pharmaceutically acceptable salts thereof, for evening dosing  
every 24 hours containing from about 180 mg to about 420 mg of the form of  
Diltiazem with excipients to provide controlled (sustained) release of the  
20 form of Diltiazem from the preparation for providing a  $C_{max}$  of Diltiazem in  
the blood at between about 10 hours and about 17 hours ( $T_{max}$ ) after  
administration of the preparation, the preparation being in a sustained-  
release dosage form in which the Diltiazem is adapted to be control released  
after administration of the preparation over a period of time wherein the  
25 preparation comprises a plurality of microgranules, each microgranule  
comprising a central core containing the form of diltiazem coated with a

microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

5 (i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

10

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

15

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

20

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants wherein the core and membrane comprise:

25

% W/W

(a) Diltiazem hydrochloride

69 - 73

	(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
	(c)	Povidone K30	1 - 2
	(d)	Sucrose stearate (crodesta F150)	7 - 8
	(e)	Magnesium stearate NF	0.5 - 2.5
5	(f)	Talc USP	0.5 - 5.0
	(g)	Titanium dioxide (USP)	0.15 - 0.3
	(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
	(i)	Polysorbate 80 (tween)	0.01 - 0.025
	(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
10	(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester	
		(dry of 30%)	7 - 11
		Purified water USP	0 (used for mixing).

15 79. The method of claim 74 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

20

80. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 74 to the patient in the evening for effective treatment of the myocardial ischemia the next morning.

25



81. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

82. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

15

83. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

20

84. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

10 85. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

86. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is

20

a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and  
5 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

87. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a  
10 microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

88. The method of claim 1 in tablet form wherein the preparation  
15 releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt

thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

89. The method of claim 1 in capsule form wherein the  
5 preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the  
10 wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15 90. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a  
20 microporous membrane and the central core comprises Diltiazem or

pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the  
5 pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

91. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule  
10 comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem  
15 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

92. The method of claim 1 in tablet form wherein the preparation  
20 releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

10

93. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a

20

water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

5

94. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule  
10 comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem  
15 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic  
20 acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

95. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or  
5 pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the  
10 pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

15

96. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central  
20 core containing the form of diltiazem coated with a microporous membrane



and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

97. The method of claim 1, in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions

which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the  
5 preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

98. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total  
10 amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and  
15 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-  
20 dispersible or water-soluble polymer and a water-, acid- and base-insoluble

polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

- 5 99. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent
- 10 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-
- 15 dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

100. The method of claim 1 in tablet form wherein the preparation  
a diffusion controlled preparation and wherein each microgranule  
comprising a central core containing the form of diltiazem coated with a  
microporous membrane and the central core comprises Diltiazem or  
5 pharmaceutically acceptable salt thereof associated with a wetting agent  
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent  
wherein the wetting agent assists to maintain the solubility of the Diltiazem  
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the  
pH of the gastrointestinal tract or other adverse conditions which the  
10 composition will meet therein and wherein the membrane comprises a water-  
dispersible or water-soluble polymer and a water-, acid- and base-insoluble  
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic  
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation  
wherein the membrane further comprises hydroxypropylmethylcellulose.

15

101. The method of claim 1 in capsule form wherein the  
preparation is a diffusion controlled preparation and wherein each  
microgranule comprising a central core containing the form of diltiazem  
coated with a microporous membrane and the central core comprises  
20 Diltiazem or pharmaceutically acceptable salt thereof associated with a

wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions

5 which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises

10 hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low

15 concentration outside).

102. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is

20 a diffusion controlled preparation and wherein each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent

5 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

10 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid

15 penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

103. The method of claim 1, in tablet form wherein the preparation

20 is a diffusion controlled preparation and wherein each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent

5 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

10 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid

15 penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

104. The method of claim 1 in tablet form wherein the preparation

20 releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).



105. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises  
5 Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions  
10 which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises  
15 hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low  
20 concentration outside) wherein the preparation contains 180 mg of Diltiazem.

106. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is

5 a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent

10 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

15 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid

20 penetrates and hydrates the bead, and dissolves the diltiazem and wetting

agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

- 5    107.    The method of claim 1                      in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent
- 10    wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-
- 15    dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when
- 20    put in gastrointestinal fluid causes the membrane to swell while fluid

penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

5

108. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central  
10 core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the  
15 solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic  
20 acid methyl ester which hydrates the preparation wherein the membrane

further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a  
5 concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

109. The method of claim 1 in capsule form wherein the  
10 preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the  
15 wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-  
20 insoluble polymer of a neutral acrylic polymer including a neutral copolymer

of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the  
5 membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

10 110. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a  
15 microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the  
20 pH of the gastrointestinal tract or other adverse conditions which the

composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation  
5 wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane  
10 (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

111. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule  
15 comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem  
20 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the

pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the Diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

112. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed



(in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and

5 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane

10 hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of

15 Diltiazem.

113. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem

20 coated with a microporous membrane and the central core comprises

Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is  
5 unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the  
10 preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration  
15 gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

114. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total  
20 amount of active per hour during dissolution, and wherein the preparation is

a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and  
5 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-  
10 dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when  
15 put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

115. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or  
5 pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the  
10 composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and  
15 wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the  
20 preparation contains 420 mg of Diltiazem.

116. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion  
5 controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists  
10 to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic  
15 polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the  
20 bead, and dissolves the diltiazem and wetting agent and benefits from a

- 120 -

concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.